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Hypoplastic Thymus and T-Cell Reduction in EECUT Syndrome

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We report on a patient with EEC/EECUT syndrome and concomitant hypoplasia of the thymus and reduction of T cells in secondary lymphatic organs. The patient was born prematurely at 35 weeks of gestational age and exhibited ectodermal dysplasia, ectrodactyly, cleft palate and urinary tract abnormalities. On the left side, a large ureterocele was present. On the right side, an atretic ureter was found. Both conditions had led to intrauterine hydronephrosis, renal dysplasia, oligohydramnios, pulmonary hypoplasia, and death of the child. Ureteral malformations are thought to be of epithelial origin. Autopsy showed only small rudiments of thymic tissue containing single epithelial cells, but were completely devoid of Hassall corpuscules. Again, this clearly points to an ectodermal defect. Although there was severe reduction of T cells in secondary lymphatic organs, the thymic defect would not have necessarily led to immunological deficiency; perhaps this is the reason that an epithelial defect in the thymus of patients with EEC syndrome has not yet been reported. With regard to an updating of the diagnosis of the EEC/EECUT syndrome, an "EEC/EECUT plus" syndrome is suggested. Am. J. Med. Genet. 69:65–68, 1997.

KEY WORDS: EEC syndrome; malformation of ureter; dysplasia of kidney; hypoplasia of thymus; immunodeficiency

INTRODUCTION

We report on a patient with ectrodactyly, ectodermal dysplasia, and cleft lip and/or palate (EEC) syndrome [Rodini and Richieri-Costa, 1990; Fosko et al., 1992]. The combination with urinary tract pathology has been termed EECUT syndrome [Hecht, 1985; London et al., 1985]. In our patient, kidney dysplasia and lung hypoplasia caused the death of the patient perinatally. The infant was also found to have severe hypoplasia of the thymus with hypoplasia of secondary lymphatic organs.

CLINICAL REPORT

The first pregnancy of a 30-year-old woman had been uneventful up to the 30th week of gestational age when a routine ultrasonographic examination showed cystic enlargement of both kidneys. There was no history of renal cysts in the family. Follow-up ultrasound studies showed enlargement of the cysts bilaterally; the lungs were suspected to be hypoplastic. During the 34th week, the mother developed signs of preeclampsia and pregnancy was terminated at 35 weeks via caesarean section. The child died 90 minutes post partum due to respiratory insufficiency. The karyotype was 46,XY.

ANATOMOPATHOLOGICAL EXAMINATION

Integument

The 2,425-g male child had a round head with a small triangular mouth and flattened tip of the nose. The palpebral fissures were small (blepharophimosis), but synechia did not exist (Fig. 1a,b). Eyelashes, eyebrows, scalp hair, and lanugo were absent. The nails on fingers and toes were severely hypoplastic. The erythematous skin was partly covered with scales. Microscopically, the epidermal layer and the dermis were thin, hair shafts were degenerating, sebaceous glands were absent and sweat glands were severely hypoplastic (Fig. 2). The erythematous aspect was caused by the dilatation of capillaries within the papillary layer of the dermis; there were no inflammatory infiltrates.

There was bilateral syndactyly of the fourth and fifth toes (Fig. 1c). On the left, there was syndactyly of the first and second toe, while the third toe was absent (ectrodactyly).

The external genitalia were male with a small penis and hypospadias. There was a wide cleft of soft and hard palate.

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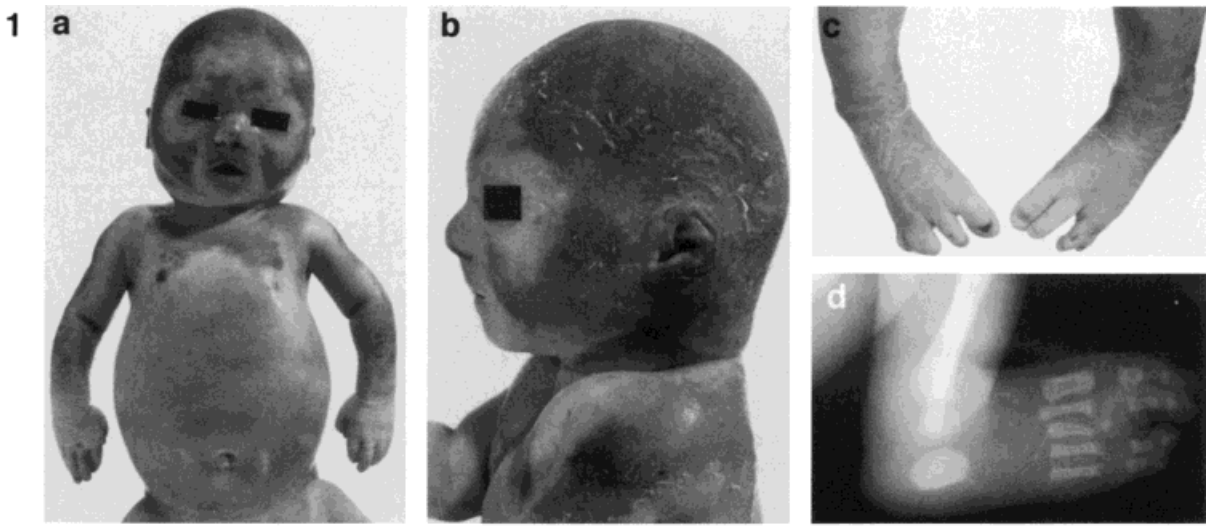

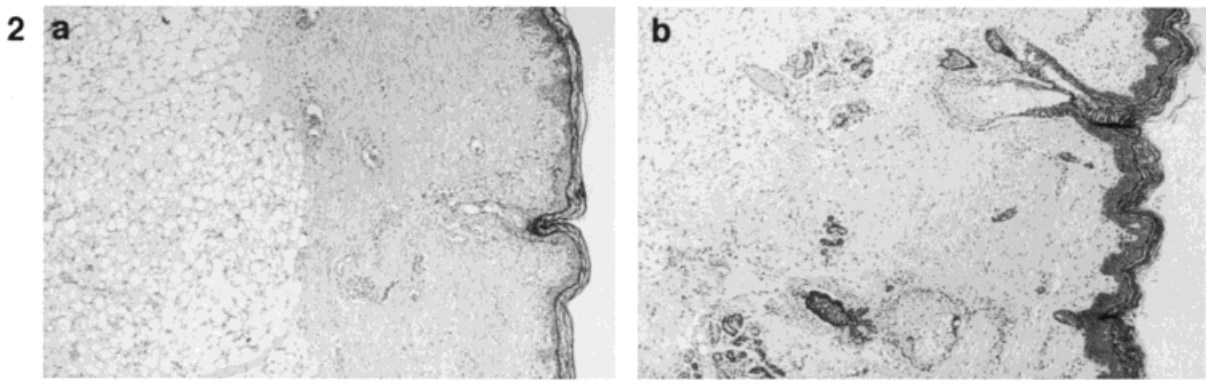

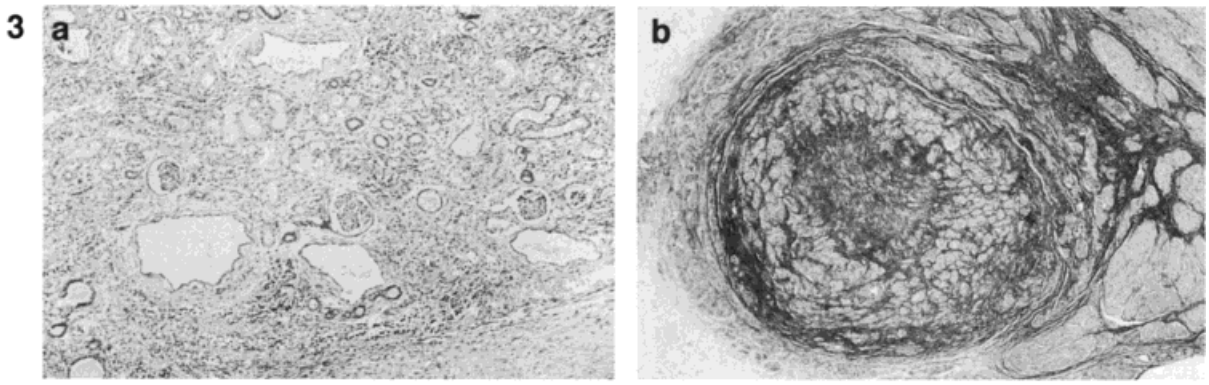

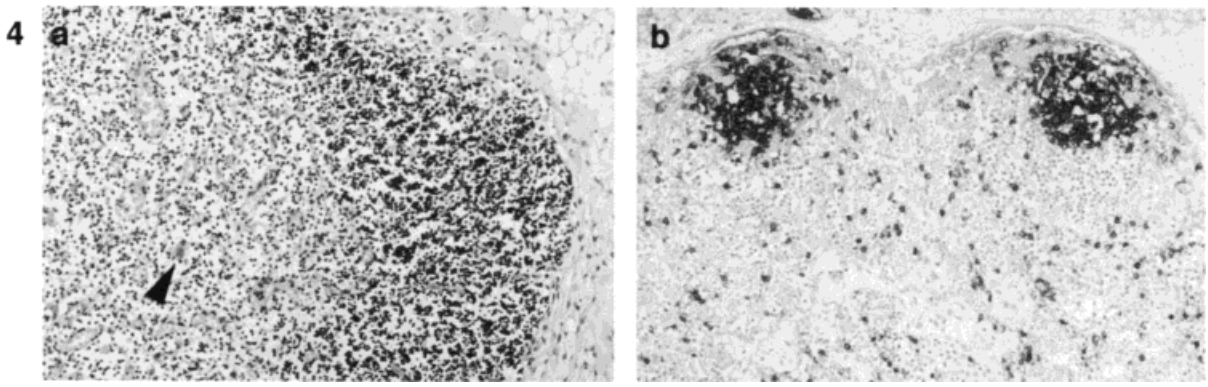

Figs. 1–4

Skeleton

Radiological examination showed a reduced diameter of the rib cage in its upper portion. The ectrodactyly on the left foot involved hypoplasia of the third metatarsal, rudimentary basal phalanx and complete lack of the distal phalanges (Fig. 1d).

Urinary Tract

The abdomen was distended due to enlargement of the kidneys which had a combined weight of 3 times the normal. Microscopic examination showed cysts, which had their origin from tubuli as well as glomeruli (Fig. 3a). Glomeruli were severely reduced in numbers; thus, the total thickness of the cortex was diminished. The medulla showed augmentation of connective tissue around tubular structures. On the left side there was a large ureterocele at the ostium which had occluded passage to the bladder. The ureter was strongly dilated and the renal pelvis had ruptured leading to perirenal urinoma. On the right side, the ureter was solid. The architecture of the ureteral wall was still recognisable on microscopic examination; however, the lumen was obliterated in the distal third of the ureter (Fig. 3b). The bladder was small; the urethra could be passed easily with a probe. The penis was bent downward with the urethral orifice of the hypospadias in the mid portion of the shaft.

Both lungs were hypoplastic with a combined weight of 29 g (instead of 61 g). Microscopic examination showed an alveolar radial count of 2 (normal range: 3.7–4.1 at 35 weeks).

Thymus, Spleen, and Lymph Nodes

The thymus was absent. Serial sectioning of tissues between pericardial sac and thyroid demonstrated several small islands of thymic tissue with the largest measuring 3 mm in diameter. Histologic study showed a distinct corticomedullary boundary with a dense lymphocyte population in the cortex. Immunohistochemically, these cells were T lymphocytes (CD 3^+). The medulla showed a less dense population of T lymphocytes with interspersed B lymphocytes (CD 20^+), which is normal in fetal thymus. However, Hassal corpuscules were absent, and only a few epithelial cells could be found with the help of anticytokeratin immunostaining within the medulla (Fig. 4a). We found several lymphnodes with a diameter of up to 6 mm containing primary follicles with normal numbers of B-cells; however, the paracortical T-cell region was only very sparsely populated (Fig. 4b). Follicles in the spleen were smaller than usual at that age. More impressive was the reduction of T cells in the periarteriolar region. Despite this reduction of lymphocytes, the weight of the spleen, 12 g, was two times normal due to an augmentation and activation of the red pulp representing extramedullary erythropoiesis.

DISCUSSION

Ectodermal dysplasia with syndactyly and cleft palate is not only seen in the EEC syndrome but also in Rapp-Hodgkin syndrome [Rapp and Hodgkin, 1968] and AEC syndrome [Hay and Wells, 1976]. Both the EEC and the Rapp-Hodgkin syndrome can present with urinary tract malformation. However, the ectrodactyly seen in one foot of our patient strongly favors the EEC syndrome [Rodini and Richieri-Costa, 1990]. In Rapp-Hodgkin syndrome a midface hypoplasia is constant; this was not found in our patient. Ectrodactyly and genitourinary anomalies are absent in AEC syndrome (ankyloblepharon-ectodermal defects-cleft lip and palate); instead, the filiform strands bridging the palpebral fissures are regarded a specific anomaly; they were not present in our patient.

The autosomal dominant EEC syndrome is the most common of the above-mentioned conditions. In 147 cases reported so far [Fosko et al., 1992], no abnormalities of the immune system were reported. The development of the thymus and its function as a primary lymphatic organ strongly depend on the presence of epithelial cells. Thus, normal anatomy of the thymus in patients with severe ectodermal dysplasia seems to be more remarkable than the presence of a thymic epithelial defect.

In nude mice, a genetic defect is responsible for ectodermal dysplasia, which includes absence of hair and dysplasia of the thymus. The epithelial defect is the cause of and the link to severe immunodeficiency observed in these mice. However, thymic epithelium is not only derived from ectoderm, but also from entoderm.

In our patient, there is development and maturation of T cells in the thymic rudiments with only a quantitative defect in secondary lymphatic organs. Lymph nodes and spleen have significantly lower numbers of lymphocytes and this reduction affects the T-cell regions. However, this would not necessarily have led to overt immunological deficiency.

The cystic dysplasia of both kidneys in our patient was caused by the obstruction of urine flow to the bladder. On the left side, this was due to a large ureterocele. In 1927, Chwalla reported a temporary membranous occlusion of the ureteral buds during the 37th to the 43rd day of human pregnancy as the cause of an ureterocele. In this short period, epithelial cells form a membrane, which is multilayered on the 39th day and dou-

Fig. 1. **a,b:** External appearance and radiology: round head with erythema, scaling and absent hair; small palpebral fissures, small triangular mouth and flattened tip of the nose. **c,d:** Both feet with syndactyly 4/5 and ectrodactyly of the 3rd toe left side.

Fig. 2. Histology of the skin. **a:** Ectodermal dysplasia is reflected by degeneration of hair follicles, rudimentary sebaceous glands and hypoplastic sweat glands. **b:** Age-matched control skin has more epithelial layers in the epidermis while the dermis is much thicker and contains completely developed appendages. (H&E, ×50).

Fig. 3. Urinary tract pathology. **a:** Kidneys with cystic dilatations of glomeruli and tubuli; augmentation of mesenchymal tissue which contains extramedullary hematopoiesis. **b:** Kidney changes are caused by obstruction, which on the right side is due to a completely obliterated lumen of the ureter. (H&E, ×60 (a), ×30 (b)).

Fig. 4. Immune system. **a:** Rudiments of thymic tissue show cortex and medulla. Hassal corpuscles are absent; only very few epithelial cells (arrow) are present. **b:** Lymph nodes, consecutively, exhibit strongly reduced numbers of T lymphocytes. The numbers of B lymphocytes, which are stained dark by immunohistochemical detection of the B-cell antigen CD 20, appeared to be normal. (×125).

ble-layered on day 47. The persistence of this membrane may be an intrinsic epithelial defect which causes a so-called stenotic ureterocele. Others have suggested a mesenchymal defect as the primary defect in ureteroceles [Weiss, 1988] because abnormal differentiation of muscle fibers had been observed with various techniques [Tanagho et al., 1965; Tokunaka et al., 1981]. Again, others have stressed pathologic innervation as the prime pathogenetic factor [Friedrich et al., 1987]. Ureteroceles, both sporadic and in EEC syndrome, may thus be the result of bidirectional acting influences of epithelial and mesenchymal cells.

The complete obliteration of the distal third of the ureteral lumen on the right was a very unusual finding. During embryonic development, the ureter undergoes a physiological obstruction and recanalization within the 7th and 8th week of pregnancy [Alcaraz et al., 1989, 1991]. Recanalization occurs during the time of extensive longitudinal growth and starts in the middle of the ureter [Ruano-Gil et al., 1975]. Again, a defect in the differentiation of epithelial cells might well be the cause for the persistence of an obliterated segment in the ureter.

Experimental work has shown that reabsoption of the ureteric intraluminal epithelium can be inhibited by hypovitaminosis A [Wilson and Warkany, 1948]. Monie [1957], inducing pteroil glutamic acid deficiency in rats, showed a delay in reabsorption of the ureterovesical membrane. Furthermore, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin causes occlusion of the ureter in rats [Abbot et al., 1987] due to hyperplasia of the luminal epithelium leading to hydroureter and hydronephrosis. These experiments clearly demonstrated that primary damage to the epithelium can cause ureteral obstruction.

The morphological findings in our case demonstrate that the epithelial defect underlying the EEC syndrome can affect many organs with widespread consequences. Several patients have been reported with an oligosymptomatic form of the dominantly inherited EEC syndrome, which was then designated as "EEC sine" syndrome [Küster et al., 1985; Majewski and Küster, 1988]. Hecht [1985] proposed the term EECUT syndrome in cases with urinary tract involvement, as outlined by London and colleagues [1985]. Our patient exhibits the complete picture of the disorder plus additional pathology in the thymus. Thus, our case with an "EEC/EECUT plus" adds a new dimension to the variability of the syndrome.

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REFERENCES

Abbott BD, Birnbaum LS, Pratt RM (1987): TCDD-induced hyperplasia of the ureteral epithelium produces hydronephrosis in murine fetuses. Teratology 35:329–334.

Alcaraz A, Vinaixa F, Tejedo-Mateu A, Forés MM, Gotzens V, Talbot-Wright R, Alvarez-Vijande R, Carretero P (1989): Enfermedad obstructiva congenita del ureter. Actas Urol Esp 13:318–322.

Alcaraz A, Vinaixa F, Tejedo-Mateu A, Forés MM, Gotzens V, Mestres CA, Oliveira J, Carretero P (1991): Obstruction and recanalization of the ureter during embryonic development. J Urol 145:410–416.

Chwalla R (1927a):The process of formation of cystic dilatation of the vesical end of theureter and of diverticula at the ureteral ostium. Urol Cutan Rev 31:499–504.

Chwalla R (1927b): Ueber die Entwicklung der Harnblase und der primären Harnröhreder Menschen mit besonderer Berücksichtigung der Art und Weise, in der sich die Ureteren von den Urnierengängen trennen, nebst Bemerkungen über die Entwicklung der Müllerschen Gänge und des Mastdarms. Z Anat Entw Gesch 83:615–733.

Felding IB, Björklund LJ (1990): Rapp-Hodgkin ectodermal dysplasia. Pediatr Dermatol 7:126–131.

Fosko SW, Stenn KS, Bologna JL (1992): Ectodermal dysplasias associated with clefting: Significance of scalp dermatitis. J Am Acad Dermatol 27:249–256.

Friedrich U, Schreiber D, Gottschalk E, Dietz W (1987): Die Ultrastruktur des distalen Ureters bei kongenitalen Malformationen im Kindesalter. Z Kinderchir 42:94–102.

Hay RJ, Wells RS (1976): The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: An autosomal dominant condition. Br J Dermatol 94:277–289.

Hecht F (1985): Updating a diagnosis: The EEC/EECUT syndrome. [Editorial]. Am J Dis Child 139:1185.

Küster W, Majewski F, Meinecke P (1985): EEC syndrome without ectrodactyly? Report of 8 cases. Clin Genet 28:130–135.

London R, Heredia RM, Israel J (1985): Urinary tract involvement in EEC syndrome. Am J Dis Child 139:1191–1193.

Majewski F, Küster W (1988): EEC syndrome sine sine? Report of a family with oligosymptomatic EEC syndrome. Clin Genet 33:69–72.

Monie IW, Nelson MM, Evans HM (1957): Abnormalities of the urinary system of rat embryos resulting from transitory deficiency of pteroilglutamic acid during gestation. Anat Rec 127:711–723.

Rapp RS, Hodgkin WE (1968): Anhidrotic ectodermal dysplasia: Autosomal dominant inheritance with palate and lip anomalies. J Med Genet 5:269–272.

Rodini ESO, Richieri-Costa A (1990): EEC syndrome: Report on 20 new patients, clinical and genetic considerations. Am J Med Genet 37:42–53.

Ruano-Gil D, Coca-Payeras A, Tejedo-Mateu A (1975): Obstruction and normal recanalization of the ureter in the human embryo: Its relation to congenitalureteric obstruction. Eur Urol 1:287–293.

Tanagho EA, Hutch JA, Meyers FH, Rambo ON (1965): Primary vesicoureteral reflux: Experimental studies of its etiology. J Urol 87:670.

Tokunaka S, Gotoh T, Koyanagi T, Tsuji I (1981): Morphological study of the ureterocele: A possible clue to its embryogenesis as evidenced by a locally arrested myogenesis. J Urol 126:726–729.

Weiss JP (1988): Embryogenesis of ureteral anomalies: A unifying theory. Aust NZ J Surg 58:631–638.

Wilson JG, Warkany J (1948): Malformation in the genitourinary tract induced by vitamin A deficiency in the rat. Am J Anat 83:357–395.